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Health and Environmental Effects Profile for Gamma-Butyrolactone

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR GAMMA-BUTYROLACTONE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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16. ABSTRACT

The Health and Environmental Effects Profile for gamma-butyrolactone was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for gamma-butyrolactone.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

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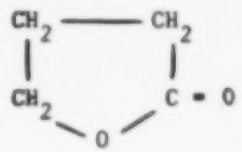
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
CNS	Central nervous system
DNA	Deoxyribonucleic acid
LD_{50}	Dose lethal to 50% of recipients
RNA	Ribonucleic acid

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

γ-Butyrolactone is known by many other names; some of the more common ones includethe following: 1,4-butanolide; butyric acid lactone; dihydro-2 (3H)-furanone; 4-butyrolactone; 4-hydroxybutanoic acid; and γ-hydroxybutyric acid cyclic ester (NIOSH, 1983; IARC, 1976). Commercial production of this compound was first reported in the United States in 1953 (IARC, 1976). The structure of γ-butyrolactone is depicted below:



Molecular formula: $C_4H_6O_2$

Molecular weight: 86.1

The Chemical Abstract Service (CAS) Registry Number for this compound is 96-48-0.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

γ-Butyrolactone is an oily liquid with a pleasant odor that is stable at pH 7. It is rapidly hydrolyzed by bases, slowly hydrolyzed by acids and reactive with inorganic acids and bases, and alcohols and amines (IARC, 1976). Some of the physical properties of this compound are listed below:

Boiling point:	206°C at 760 mm Hg; 89°C at 12 mm Hg (IARC, 1976)
Melting point:	-42°C (IARC, 1976)
Density:	d_0^{16} 1.1286 (IARC, 1976)
Refractive index:	n_D^{20} 1.4341 (IARC, 1976)
Solubility:	miscible with water, ethanol, acetone and benzene (IARC, 1976); completely soluble in water at 25°C (Weast, 1972)
Spectroscopy data:	λmax 209 nm (IARC, 1976)

Log octanol/water partition coefficient:	-0.64 (Hansch and Leo, 1979)
Vapor pressure:	50.1 mm Hg at 119°C; 79.4 mm Hg at 132°C; 199.6 mm Hg at 159°C (McKinley and Copes, 1950).

1.3. PRODUCTION DATA

γ-Butyrolactone can be prepared by the dehydrogenation of 1,4-butanediol over a copper catalyst at 200-250°C (IARC, 1976) or by high-pressure synthesis from acetylene and formaldehyde (Hawley, 1977).

Table 1-1 shows the producers of γ-butyrolactone before 1977 as listed in the TSCA production file (U.S. EPA, 1983).

SRI (1983) lists GAF Corporation as the sole producer of γ-butyrolactone as of January, 1983.

1.4. USE DATA

γ-Butyrolactone is an intermediate in the production of pyrrolidone. It is also used as a solvent for agricultural chemicals and polymers; as a dyeing and painting agent; as a paint remover; in inorganic synthesis; as an electrolyte in lithium batteries; and as a starting product for 2,4-dichlorophenoxy butyric acid (IARC, 1976; Bach, 1978; Hawley, 1977).

The estimated consumption of γ-butyrolactone in the United States was 28-32 million pounds in 1974 (SRI, 1976).

TABLE 1-1

Production of γ-Butyrolactone[a]

Producer	Location	Production Volume (lbs/year)
Elan Chemical Co.	Newark, NJ	NR
Union Carbide Co.	Brownsville, TX	NR
GAF Corporation	Calvert City, KY	NR
CIBA-Geigy Corp.[b]	Ardsley, NY	No production in 1977
Celanese Chemical Co.	Pampa, TX	10,000,000-50,000,000
Hydron Laboratories	New Brunswick, NJ	<1,000
BASF Wyandotte Corp.[b]	Parsippany, NJ	100,000-1,000,000

[a]Source: U.S. EPA, 1983

[b]Reported as an importer

NR = Not reported

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

The fate of γ-butyrolactone in the atmospheric environment is likely to depend on its ability to undergo photochemical or chemical reactions. Simonaitis and Pitts (1971) irradiated γ-butyrolactone in the vapor phase at 125°C with a medium-pressure mercury lamp (effective wavelengths 210-260 nm) and found that it isomerized to succinaldehyde, and underwent a fragmentation reaction to give ethylene, carbon monoxide, formaldehyde, propylene or cyclopropane and carbon dioxide. However, atmospheric γ-butyrolactone may not undergo photochemical reactions under natural sunlight since this compound does not absorb light above 290 nm (Weast, 1972). Pertinent data regarding the significance of γ-butyrolactone undergoing chemical reactions in the atmosphere were not located in the available literature (see Appendix).

γ-Butyrolactone is completely soluble in water at 25°C (Weast, 1972) and is rapidly hydrolyzed by bases and slowly hydrolyzed by acids (IARC, 1976); no information is available on hydrolysis at pH 7. γ-Butyrolactone may undergo photochemical reactions in the aqueous environment. Simonaitis and Pitts (1968) reported that the products obtained from the irradiation of γ-butyrolactone in solution with a mercury resonance lamp (253.7 nm at 25°C) were allyl formate, succinaldehyde, cyclopropane, CO_2 and small amounts of ethylene, propylene and carbon monoxide. However, photochemical reactions in natural aquatic environments seem improbable, as the compound does not absorb light above 290 nm (Weast, 1972).

Microbial degradation may contribute to the disappearance of this chemical from the aqueous media. van der Linden and Huybregtse (1967) identified a strain of Pseudomonas aeniguiosa that was capable of oxidizing γ-butyro-

lactone when cells were treated or grown on 1,6-hexanediol. Whether degradation by bacteria will be a significant process in the natural environment is difficult to determine from this study.

Based on the log octanol-water partition coefficient (-0.64) (Hansch and Leo, 1979) for γ-butyrolactone, it is unlikely that this compound will bioaccumulate in aquatic organisms.

Pertinent data regarding the fate and transport of γ-butyrolactone in the soil were not located in the available literature (see Appendix); however, based on the relatively high water solubility and low octanol-water partition coefficient of this compound, γ-butyrolactone may likely leach through the soil column or dissociate in basic or acidic soils.

3. EXPOSURE

Monitoring data for γ-butyrolactone in the environment were not encountered in STORET; however, a number of cases were reported where this compound was detected in food. Levels of 2 mg/ℓ were detected in beer (Spence et al., 1973) and 5-31 mg/ℓ were found in apple brandy (Rudali et al., 1976). γ-Butyrolactone has also been found in other foods such as whey (Ferretti and Flanagan, 1971), vinegar (Kahn et al., 1972), wine (Webb et al., 1964), cooked meats (Liebich et al., 1972; Gordon, 1972), roasted filberts (Sheldon et al., 1972), coffee (Gianturco et al., 1966) and tomatoes (Johnson et al., 1971).

4. PHARMACOKINETICS

4.1. ABSORPTION

Lettieri and Fung (1978) reported that γ-butyrolactone was rapidly and extensively absorbed from the gastrointestinal tract of rats. Administration by gavage of 136 mg/kg or 546 mg/kg (6.34 mmole/kg) γ-butyrolactone to rats resulted in peak plasma levels of >300 and >1000 μg/mℓ, respectively. Peak levels were maintained for almost 3 hours at the 546 mg/kg dose level. The method of analysis did not distinguish between the parent compound and a metabolite, γ-hydroxybutyric acid. Similar results were reported in an abstract by Lettieri (1978). Following oral administration of an unspecified amount of radiolabeled γ-butyrolactone to rats, the compound was completely and rapidly absorbed from the gastrointestinal tract. The author also stated that previous reports on the concentrations of γ-butyrolactone were unreliable because of the nonspecificity of the assay used; however, it is unclear to which study he was referring.

Approximately 10% of a percutaneous dose of 6.34 μmoles/kg γ-butyrolactone was absorbed from the shaved skin of rats during 4 hours of exposure. The parent compound was rapidly hydrolyzed as evidenced by the detection of no γ-butyrolactone and up to 200 μg/mℓ of γ-hydroxybutyric acid in the plasma during exposure (Fung et al., 1979). The percent absorption was estimated by comparing the area under the plasma γ-hydroxybutyric acid concentration-time curve after dermal administration with that after intravenous administration.

4.2. DISTRIBUTION

Roth and Giarman (1966) reported that when 500 mg/kg γ-butyrolactone was administered intravenously to rats, approximately 12 μmoles/mℓ of γ-butyrolactone and γ-hydroxybutyric acid were present in the blood at

1 minute and 9 μmoles/mℓ were detected at 5, 15 and 30 minutes. After 15 minutes, the concentration of γ-butyrolactone and γ-hydroxybutyric acid in muscle was ~0.0035 M and in fat was ~0.001 M (Rath and Giarman, 1966). The method of analysis did not distinguish between parent compound and metabolite.

Intraperitoneal administration of γ-butyrolactone (500 mg/kg) to eight rats resulted in a very rapid increase of the parent compound in the blood, heart and kidney. Concentrations of ~4.0-4.5 μmoles/g were measured in each of these tissues within 1 hour and all levels dropped to between 0.5 and 1.0 μmoles/g after 4 hours. The increase was much slower in the muscle, brain and liver. Peak levels of ~1.7-2.0 μmoles/g were observed in the brain and muscle within 1 hour and in the liver (~2.0 μmoles/g) within 2 hours. All levels declined to ~0 within 4 hours (Beisman and Skolnik, 1964).

4.3. METABOLISM

Ingestion of γ-butyrolactone by humans resulted in the formation of S-3,4-dihydroxybutyrate, glycolate and a compound tentatively identified as the hydroxy epoxide tautomer of 4-hydroxy-3-oxo-butyrate in the urine. The results provided evidence that γ-butyrolactone is metabolized in humans to γ-hydroxybutyrate, which is further metabolized by β-oxidation (Lee, 1977).

Following intravenous administration of 500 mg/kg of 1-^{14}C-γ-butyrolactone to rats, the compound was metabolized in ~20 minutes to CO_2 (Roth and Giarman, 1966).

γ-Butyrolactone was hydrolyzed by the enzyme lactonase to γ-hydroxybutyric acid *in vitro* by the blood serum of rats. The half-time of conversion was <1 minute (Roth and Giarman, 1966). Rapid hydrolysis also occurred *in vitro* with the liver of rats and more slowly with the plasma of cats (Roth and Giarman, 1966).

According to Bessman and Skolnik (1964), however, following intraperitoneal administration of γ-butyrolactone to rats, the parent compound was found in the blood and tissues (see Section 4.2). The only tissue in which γ-hydroxybutyric acid levels were increased was the brain. Levels of the acid in brain tissue were lower than were levels of the lactone, and the time course of narcosis paralleled the time course of γ-butyrolactone levels in the brain. When the sodium salt of γ-hydroxybutyric acid was administered, both the parent compound and γ-butyrolactone were found in the blood and tissues. These results indicated that the lactone and the acid were interconvertible, and that the lactone might be responsible for narcosis.

γ-Butyrolactone did not form a thioester when incubated with either glutathione or cysteine in vitro (Dijkstra, 1975).

4.4. EXCRETION

Ingestion by humans of 1.0 g γ-butyrolactone dissolved in water resulted in the excretion of S-3,4-dihydroxybutyric acid and glycolic acid in the urine. A compound tentatively identified as the hydroxy epoxide tautomer of 4-hydroxy-3-oxobutyric acid was also excreted. The estimated total excretion of these compounds was ~100-200 mg in 5 hours (Lee, 1977).

Following intravenous administration of 500 mg/kg of 1-^{14}C-γ-butyrolactone to rats, ~60% of the total radioactivity was recovered within ~2.5 hours in the respired air. A peak in the respiratory CO_2 was reached in ~20 minutes (Roth and Giarman, 1966).

In rats, administration of 1-^{14}C or 4-^{14}C-hydroxybutyrate by inhalation resulted in the excretion of $^{14}CO_2$; ~66% of the radioactivity was excreted as $^{14}CO_2$ in 6 hours and an additional 10-20% within the next 18 hours (Walkenstein et al., 1964).

5. EFFECTS

5.1. CARCINOGENICITY

γ-Butyrolactone has not produced carcinogenic effects in either rats or mice treated by the oral, dermal or subcutaneous routes (IARC, 1976).

In an early study by Schoental (1968), 10 male rats were given by gavage 3-6 doses of γ-butyrolactone in water or ethanol ranging from 100-600 mg/kg/dose over a period of 7.5 months. Of the 6 rats surviving >1 year after administration of the last dose, the incidence of tumors was not significantly different from the control group, except that one treated rat had bilateral interstitial tumors of the testes and two treated rats had squamous carcinomas of the jaw. These tumors were not seen in concurrent controls and, according to the author, are rare in aging control rats.

In a study by Rudali et al. (1976) a group of 60 C3H mice of both sexes received 1000 mg γ-butyrolactone/kg in its diet for life. An additional group of 36 XVII/6 mice of both sexes was administered oral doses of 2 mg γ-butyrolactone in 0.1 mℓ water twice weekly for life. No significant increase in tumor incidence was observed when compared with control groups.

No significant increase in skin tumor incidence was observed in 30 male or 30 female Swiss ICR/Ha mice painted dermally with 100 mg (~0.1 mℓ) of a 10% solution of γ-butyrolactone in benzene or acetone thrice weekly for life (Van Duuren et al., 1963, 1965). Van Duuren also discussed these results in a later publication (Van Duuren, 1969).

A group of 30 XVII/6 mice of both sexes was given skin applications of a 1% solution of γ-butyrolactone in acetone twice weekly for life. No significant increases in incidences of lung tumors were observed when compared with controls and no skin tumors were observed (Rudali et al., 1976).

No tumors were observed in 16 female Swiss Webster mice administered 12 subcutaneous injections of 0.005 mg γ-butyrolactone in 0.1 mℓ tricaprylin. Injections were given 3 times/week for 4 weeks, followed by an observation period of 18-24 months (Swern et al., 1970).

No tumors were observed in five male Wistar rats receiving subcutaneous injections of 2 mg γ-butyrolactone in oil for 61 weeks (Dickens and Jones, 1961). Injections were given twice weekly.

γ-Butyrolactone is currently being tested by the National Toxicology Program (NTP) for carcinogenesis by standard bioassay protocol as of July, 1982.

5.2. MUTAGENICITY

γ-Butyrolactone has not been found to be genotoxic in either *in vitro* assays with bacteria and human leukocytes or *in vivo* assays with mice.

γ-Butyrolactone was not mutagenic in concentrations of up to 1.0 and 10.0 μmoles/plate in the plate-incorporation assay with *Salmonella typhimurium* (strains TA98, TA100 and TA1535) both with and without S9 (Loquet et al., 1981).

Withers (1966) found no evidence of chromosome aberrations when a concentration of 7×10^{-4} M γ-butyrolactone was incubated with human leukocytes for 72 hours.

γ-Butyrolactone was not detected as a clastogen in the *in vivo* micronucleus test with B6C3F1/Heb mice at concentrations of 0.70 mℓ/kg (Katz et al., 1981).

Negative results were obtained in the *in vivo* sperm-head abnormalities assay with (CBA o x BALB/C +)F_1 male mice at concentrations of 0.1, 0.25, 0.5 or 1.0 mg/kg/day γ-butyrolactone (Topham, 1980).

Hemminki (1981) found γ-butyrolactone to be unreactive with guanosine, RNA and DNA at a concentration of 0.286 μM.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenic potential of γ-butyrolactone were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Female Sprague-Dawley rats (5-11 rats/dose level) were administered intraperitoneally 750, 500, 250, 125 or 62.5 mg/kg γ-butyrolactone diluted with saline before estrus; 15 controls were administered saline only. Ovulatory inhibition was observed in treated rats at all dose levels. At 750 mg/kg, significant increases in uterine wet weight (luminal fluid expressed) and uterine ballooning were observed compared with controls. No change was observed in ovarian weight. γ-Butyrolactone produced a significant dose-related decrease in serum LH (luteinizing hormone). Proestrus FSH (follicle stimulating hormone) was also significantly reduced (Beattie et al., 1976).

5.5. CHRONIC TOXICITY

γ-Butyrolactone was given (3-6 doses) by gavage to 12 male rats ranging from 100-600 mg/kg in water or ethanol over 7.5 months. Of the six rats that survived >1 year after the last dose, one had degenerative lesions and calcification in the heart and kidney, several showed chronic inflammatory lung lesions with bronchiectasis and two had interstitial hyperplasia in the testes (Schoental, 1968); however, similar chronic lung and kidney lesions were encountered in the control rats.

5.6. OTHER RELEVANT INFORMATION

The following LD_{50}s have been reported for γ-butyrolactone:

oral: rats, mice:	800-1600 mg/kg/ (IARC, 1976)
oral: guinea pig:	500-700 mg/kg (IARC, 1976)
dermal: guinea pig:	5.6 g/kg (IARC, 1976)
intraperitoneal: rat:	1000 mg/kg (NIOSH, 1983)
intraperitoneal: mouse:	1100 mg/kg (NIOSH, 1983)
intravenous: rabbit:	500 mg/kg (NIOSH, 1983)

γ-Butyrolactone and its product of hydrolytic cleavage, γ-hydroxybutyric acid, are general depressants of the CNS (Nowycky and Roth, 1979). These compounds cause a prolonged unconsciousness, characterized by loss of righting reflex in rats (Giorgi and Rubio, 1981; Guidotti and Ballotti, 1970; MacMillan, 1978). They are also naturally occurring metabolites found in the mammalian brain (Roth and Giarman, 1966).

γ-Butyrolactone produced significant, dose-related depression of the rates of cerebral glucose utilization in rats when administered intravenously (Wolfson et al., 1977). Intravenous injection of 150-1200 mg/μg of γ-butyrolactone caused increased glycogen and glucose levels and decreased pyruvate, lactate, alpha-ketoglutarate and malate levels in the cerebrum of rats 60 minutes after injection. Higher doses were associated with depressions of citrate and glutamate, and acute increases of arterial CO_2 tension (MacMillan, 1978).

Single intraperitoneal injections of 750 and 1500 mg/kg γ-butyrolactone significantly increased the plasma prolactin levels of male rats (Meltzer and Fang, 1977). Plasma prolactin was measured 30 minutes after the injection.

γ-Butyrolactone has been found to be capable of penetrating human erythrocytes (<u>in vitro</u>) (Sgaragli and Zilletti, 1970; Andraud et al., 1970).

A decrease in the uptake of rubidium, an increase in potassium efflux and decreases in the levels of glutathione and lactic acid in the human erythrocytes were observed *in vitro* following the addition of γ-butyrolactone. Also, Andraud et al. (1970) observed a minor inhibitory effect on erythrocytic cholinesterase.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The effects of 5 mg γ-butyrolactone/ℓ during 24-hour exposures were examined in rainbow trout, Salmo gairdneri, bluegill sunfish, Lepomis macrochirus and larval sea lampreys, Petromyzon marinus (Applegate et al., 1957). No effect of γ-butyrolactone at the test concentration was observed in any of the three species during the static toxicity tests. Hann and Jensen (1974) reported that the median lethal concentration of γ-butyrolactone exceeded 1000 mg/ℓ (species of fish not specified).

Additional data regarding chronic aquatic toxicity, effects on aquatic plants or the occurrence of aquatic residues of γ-butyrolactone were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

According to the Code of Federal Regulations (CFR), γ-butyrolactone is exempt from the requirement of residue tolerances when used in accordance with good agricultural practice (40 CFR 180.001).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of γ-butyrolactone were not located in the available literature.

8. RISK ASSESSMENT

Researchers found no evidence that γ-butyrolactone produces carcinogenic effects in either rats or mice treated by the oral, dermal or subcutaneous routes (Schoental, 1968; Rudali et al., 1976; Van Duuren, 1969; Swern et al., 1970; Dickens and Jones, 1961). γ-Butyrolactone was not found to be mutagenic or clastogenic in *in vitro* assays with bacteria (Loquet et al., 1981) or human leukocytes (Withers, 1966) or in *in vivo* assays with mice (Katz et al., 1981; Topham, 1980).

In the chronic study of Schoental (1968), some tumors and lesions of the lung and kidneys were observed in rats given 3-6 gavage doses of γ-butyrolactone at widely spaced intervals; however, because of the small number of animals, the intermittent dosing schedule and the occurrence of similar lesions in controls, these data cannot be used for quantitative risk assessment or calculation of an ADI for γ-butyrolactone.

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

Most of these searches were conducted in May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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